REMARKS

Claims 21 and 28-45 were pending and under consideration. With this Amendment, Claim 34 has been canceled. Claims 21, 28-33 and 38-43 have been amended. Claims 46-49 have been added. After entry of the instant amendment, Claims 21, 28-33 and 38-49 are pending and under consideration. A version with markings to show changes made is attached at Exhibit A. For convenience, a clean copy of the pending claims after entry of the instant amendment is attached at Exhibit B.

I. THE AMENDMENTS TO THE CLAIMS

Claims 21, 28-33 and 38-43 have been amended to recite, in relevant part, determining the quantity of hTERT mRNA comprising β-region coding sequence using primers that hybridize within or flank the coding sequence of the β-region of the hTERT gene. Support for amended Claim 21 may be found, for example in Claims 21 and 1 as originally filed and in the specification, for example, at page 3, lines 1 to 14. Support for amended Claims 28-33 and 38-43 may be found, in the specification, for example, at page 3, lines 20 to 24; page 15, line 29 to page 16, line 14; page 20, line 14 to page 21, line 8 and page 23, line 24 to page 24, line 22.

New Claim 46 recites the method of Claim 21, wherein step (2) additionally comprises amplifying the nucleic acid sequence in the presence of a probe which hybridizes to the nucleic acid sequence. New Claim 47 recites the method of Claim 46, wherein the probe is labeled. New Claim 48 recites the kit of Claim 38, further comprising a probe which hybridizes to a sequence which is amplified by the first and second primers. New Claim 49 recites the kit of Claim 38, wherein the probe is labeled. Support for new Claims 46-49 can be found in the specification, for example, at page 16, line 21 to page 17, line 21.

As the amendments and new claims are fully supported by the specification and claims as originally filed; they do not constitute new matter. Applicants hereby request entry of the amendments into the record.

II. WITHDRAWAL OF REJECTION

The Applicants note with appreciation that rejection under 35 U.S.C. §103 based on Nakamura, *et al.*, Science 1997, 277; 955-959, is withdrawn.

III. CLAIM REJECTION UNDER 35 U.S.C. §112, First Paragraph

Claims 21, 33, 34, 38 and 42 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled as to primers which hybridize outside of exon 8. The PTO states that the specification is enabling for a method for identifying the presence of cancerous cells in a human sample using primers which hybridize within exon 8, but allegedly does not provide enablement for primers which hybridize within exon 8 (*sic*) or downstream of exon 8. Applicants respectfully submit that Claims 21, 33, 34, 38 and 42 are fully enabled by the specification.

The β-region is a 182 nucleotide sequence consisting of exons 7 and 8. *See,* specification at page 11, line 1. The specification teaches and describes amplification of the hTERT mRNA comprising β-region coding sequence, including using primers that hybridize within exon 8 and both upstream and downstream of exon 8. Amplification of hTERT mRNA comprising β-region coding sequence using primers within or flanking the β-region coding sequence are taught and described in the specification. For example, the specification describes amplification of the hTERT mRNA β-region using a pair of primers, one primer hybridizes to a sequence within exon 8 and the other primer hybridizes preferably within exon 6. (Page 3, lines 20 to 24, also cited by the PTO in paper 19 of March 27, 2002, page 3). Preferred primers are described in the specification, for example, at page 3, lines 26 to 29 and page 15, line 29 to page 16, line 20. These preferred primers are those that encompass the hTERT mRNA β-region coding sequence and provide for specific and efficient amplification of the mRNA β-region coding sequence. Preferred primers are those that hybridize within exon 8 and either upstream of exon 7 or downstream of exon 8. A particularly preferred pair of primers, SYC1118 and SYC1097, hybridize within exon 6 and within exon 8, respectively.

The specification further teaches and describes using primers that hybridize at positions both upstream and downstream of exon 8. In particular, example 2 describes that a previously unobserved splice variant was identified by amplifying hTERT mRNA using primers that flank the β-region. (Page 20, lines 14 to 16). The primers that flank the β-region are SYC1076, a downstream primer, that hybridizes within exon 6 and SYC1078, an upstream primer, that hybridizes within exon 9. Use of these primers encompassing the hTERT mRNA β-region coding sequence amplified most efficiently the β-deletion splice variant. Such efficient amplification of the β-deletion splice variant eliminates unpredictability. Applicants respectfully submit that the PTO misunderstands when it alleges

that use of these primers would provide unpredictable results. (Paper 19, page 3). The example clearly demonstrates that amplification of the hTERT mRNA comprising β-region coding sequence provides an efficient and accurate estimate of telomerase activity. (Page 23, lines 11 to 22).

Examples 3 and 4 also teach and describe the accuracy and predictability of estimating telomerase activity using primers that amplify hTERT mRNA comprising β-region coding sequence. In example 3, primers SYC1076 and SYC1097, hybridizing within exon 6 and exon 8, efficiently and uniformly amplified hTERT mRNA comprising β-region coding sequence. This uniformity provided by the primers of the invention results in more consistent and accurate quantitative estimates. (Page 25, lines 7 to 22). Example 4 teaches and describes the quantitation of hTERT mRNA using primers SYC1097 and SYC1118, hybridizing within exon 6 and exon 8. (Page 26, line 23 to page 27, line 24).

The specification teaches and describes primers that encompass the hTERT mRNA β-region coding sequence. As discussed above, primers that hybridize both upstream and downstream of exon 8 have been described with examples provided to demonstrate the accuracy and predictability of estimating telomerase activity using these primers. Applicants are perplexed by the PTO's assertion that only primers that hybridize within exon 8 are enabled. This is simply not the case. The specification and the examples therein teach and describe amplification of the hTERT mRNA β-region coding sequence using various pairs of primers. These primer pairs hybridize upstream of exon 8 and within exon 8 or downstream of exon 8. Applicants do not understand how a primer hybridizing within exon 8, can be enabled and a second primer, taught and described in the same manner, or in the same example can be rejected as allegedly not enabled. Primers that flank or encompass the hTERT mRNA β-region coding sequence are fully taught and described in the specification. Further, given the teachings of the specification, a person of skill in the art could use primers that flank the hTERT mRNA β-region coding sequence without undue experimentation.

Applicants respectfully submit that Claims 21, 33, 34, 38 and 42 are fully enabled by the specification. Applicants therefore, respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

IV. CLAIM REJECTION UNDER 35 U.S.C. §112, Second Paragraph

A. Written Description

Claims 21, 33, 34, 38 and 42 stand rejected as allegedly failing to set forth the subject matter which Applicants regard as their invention.

Applicants simply do not understand the basis for the PTO's assertion. The primers of the invention are recited in independent Claim 21 and dependent Claims 28-33, specifically Claims 30 and 32. The primers of the invention are also recited in independent Claim 38, drawn to a kit comprising the primers, and dependent Claims 39-45. Claims 41, 42 and 45 recite a kit comprising specific primers. Thus, the PTO's assertion that the critical aspect of the invention is not claimed has no support. Applicants have maintained that primers that encompass β-region coding sequence of the hTERT gene are novel. The primers of the invention are used in the claimed methods to provide an accurate and predictable measure of telomerase activity and hence the presence of cancerous cells. Applicants have described in numerous examples how the primers are used to measure hTERT mRNA comprising β-region coding sequence and the correlation with accurate predictions of the presence of cancerous cells.

The PTO asserts that the comparison between Hisatomi and the instant invention in Paper No. 9 supports the rejection under 35 U.S.C. §112, second paragraph. Applicants assertion in Paper No. 9 supports Applicants present position. That is, the position of the primers, encompassing β-region coding sequence of the hTERT gene, are distinct from, and an improvement over Hisatomi, which teaches primers that hybridize in exons 3 and 4. The primers of the present invention amplify a hTERT mRNA species that is a significantly more accurate predictor of telomerase activity and hence a more accurate indication of the presence of cancerous cells. The improved correlation between levels of hTERT mRNA comprising β-region coding sequence and telomerase activity using the primers of the invention relative to using the primers of Hisatomi is evidenced by the correlation coefficient of 0.751 for Hisatomi and 0.9805 for the present invention.

The primers of the invention are recited in independent Claims 21 and 38 and specifically in Claims 30, 32, 41, 42 and 45. Applicants therefore, respectfully submit that Claims 21, 33, 38 and 42 set forth the subject matter of the invention and respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

B. Indefiniteness

Claims 21, 28-45 stand rejected as allegedly being indefinite under 35 U.S.C. §112, second paragraph. The PTO alleges that the phrase 'capable of hybridizing' is indefinite.

Claims 21, 28, 29, 31, 33, 38-40 and 43 have been amended to recite, in relevant part, primers that hybridize within a region of the hTERT gene as suggested by the PTO.

Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

V. CLAIM REJECTIONS UNDER 35 U.S.C. §102

Claims 21, 28 and 35 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Nakamura (Molecular Carcinogenesis, 1999, 26: 312-320; hereinafter 'Nakamura-1'). The standard for anticipation under 35 U.S.C. §102 is strict identity. Anticipation under §102 can only be established by a single prior art reference that teaches each and every element of the claimed invention. *Structural Rubber Products Co. v. Park Rubber Co.* 223 USPQ 1264 (1984).

Amended Claims 21, 28 and 35 recite, in relevant part, the use of a primer that hybridizes within exon 8. The primers of Nakamura-1 differ from Applicants. Nakamura-1 describes primers U1513 and L1982, which hybridize to Exon 5/6 (positions 2175-2198) and Exon 10 (positions 2644-2667). Because the primers of Nakamura-1 do not hybridize to exon 8, Applicants respectfully submit that Nakamura-1 does not anticipate amended Claims 21, 28 and 35. Furthermore, Claims 21 and 38 recite the identification of cancerous cells based on the presence of a β-region coding sequence. Nakamura-1 does not teach or suggest any correlation between the β-region coding sequence and telomerase activity.

Applicants respectfully submit that amended Claims 21, 28 and 35 are not anticipated under 35 U.S.C. §102 (a) and respectfully request that the rejection be withdrawn.

VI. CLAIM REJECTIONS UNDER 35 U.S.C. §103 (a)

Claims 21, 31, 35-36 stand rejected as allegedly unpatentable over Cech (U.S. Patent No. 6,166,178, December 26, 2000; hereinafter 'Cech') in view of Kilian (Molecular Genetics, 1997, 6(12): 2011-2019; hereinafter 'Kilian'). Claims 28-30, 32, 35-37 stand rejected as allegedly unpatentable over Cech in view of Kilian in view of Nakamura (Genbank Accession Number AF015950, August 1997; hereinafter 'Nakamura-2').

Claims 21, 28-32 and 35-37 stand rejected as allegedly unpatentable over Kilian in view of Hisatomi (International J Oncology, 1999, 14: 727-732; hereinafter 'Hisatomi') in view of Nakamura-2. Claims 21, 28-32 and 35-37 stand rejected as alleged unpatentable over Kilian in view of Meyerson (Cell, 1997, 90: 785-795; hereinafter 'Meyerson') in view of Nakamura-2. Claims 38-45 stand rejected as allegedly unpatentable over Kilian in view of Nakamura-2 in view of Meyerson in view of Stratagene Catalog (1988; hereinafter 'Stratagene').

Applicants respectfully traverse these rejections. Applicants have discovered that detection and quantitation of hTERT mRNA encoding the β-region allows selective measurement of mRNA encoding an active hTERT protein. (Page 3, lines 6 to 8). Thus, the active hTERT protein, and more specifically, gene products encoding an active hTERT protein, provide an accurate measure of telomerase activity. This in turn allows an improved marker for cancer diagnosis. (Page 3, lines 15 to 19).

None of the references cited by the Patent Office teaches or describes that gene products of the β-region of the hTERT gene is an accurate measure of telomerase activity.

A. <u>The Cited References</u>

The Patent Office has repeatedly cited Kilian, Nakamura-2, Hisatomi, Meyerson and Stratagene as the basis for rejection under 35 U.S.C. §103. In addition, in the Office Action mailed March 27, 2002, the Patent Office also cited Cech. Applicants have carefully studied the above cited references and respectfully disagree with the Patent Office's conclusion that they pose a barrier to patentability.

The references cited by the Patent Office do not teach or suggest that hTERT mRNA comprising a β-region coding sequence is an accurate marker for telomerase activity. The specification teaches that an accurate and reproducible measure of telomerase activity is provided by selectively measuring mRNA splice variants that encode the β-region of hTERT, an active protein. (Page 2, lines 27 to 29). Several splice variants of the hTERT gene have been reported, some of which encode for active hTERT β-region protein and some of which encode for other forms. (Page 3, lines 2 to 8). Applicants have discovered that gene products encoding an active hTERT β-region protein provide an accurate marker for telomerase activity. (Page 3, lines 6 to 14, Example 7 at page 38, line 5 to page 39, line 21). In addition, the primers and probes claimed are but one aspect of Applicants' invention, not the sum of Applicants' invention, as suggested by the Patent Office.

Although the Patent Office has been thorough in their examination, Applicants respectfully submit that the Patent Office has yet to cite a single reference teaching or suggesting the quantitation of mRNA of the β-region of the hTERT gene as an accurate and reproducible measure of telomerase activity. Nor has the Patent Office provided a single reference teaching or suggesting the primers and probes used for detection and quantitation of mRNA of the β-region of the hTERT gene.

i. Kilian

Kilian teaches a number of variant hTCS 1 transcripts, including Insertions 1, 2 and 3 and α and β-Deletions. (Page 2016, Figure 5). Kilian teaches that telomerase is expressed in *several normal tissues*, telomerase positive immortal cell lines and *various tumors*. (Abstract, emphasis added). Kilian also teaches that telomerase is not expressed in the majority of non-immortal and telomerase negative immortal cell lines. In addition, Kilian teaches that "the P-loop present within the 182 bp fragment (spliced exon β) that is present only in a subpopulation of the mRNA in most RNA samples analyzed and *completely absent from several tumor samples*." (Page 2017, column 1, emphasis added). Thus Kilian teaches away from the claimed invention because Kilian teaches an inconsistent relationship between the hTERT β-region gene products, in particular, mRNA, and the accurate measure of telomerase activity and an accurate identification of cancerous cells.

ii. Nakamura-2

Nakamura-2 describes the nucleic acid sequence of the hTERT gene coding region. Nakamura-2 does not teach or suggest quantifying β-region containing gene product for the purpose of detecting telomerase activity and accurately identifying cancerous cells.

iii. Hisatomi

Hisatomi teaches a general correlation between hTERT mRNA and telomerase activity in hepatocellular carcinoma. Hisatomi does not teach or suggest that quantifying gene products encoding the β-region provides an accurate and reproducible measure of telomerase activity. (See also, Section IV, A, above).

iv. Meyerson

Meyerson teaches a *general correlation* between hEST2 (telomerase catalytic subunit)

mRNA levels and assayable telomerase activity. (Page 793, col. 1, 2nd paragraph, emphasis added). Meyerson does not teach or suggest that quantifying gene products encoding the β-region provides an accurate and reproducible measure of telomerase activity.

v. **Stratagene**

The Stratagene Catalog describes commercially available reagents in kit form. Stratagene does not teach or suggest an accurate and reproducible method of determining telomerase activity by determining hTERT mRNA comprising a β-region coding sequence.

vi. **Cech**

Cech describes one embodiment as a " Δ182 hTRT" polynucleotide, which correlates with the β-region. (Column 20, line 40). However, Cech does not teach or suggest that gene products encoding a β-region ("Δ 182" hTRT polynucleotide) correlate with telomerase activity thereby providing an accurate marker.

Thus, neither Kilian Nakamura-2, Hisatomi, Meyerson, Stratagene or Cech alone or in any combination teach or suggest that hTERT mRNA comprising a β-region coding sequence is an accurate marker for telomerase activity. Neither Kilian, Nakamura-2, Hisatomi, Meyerson, Stratagene nor Cech alone or in any combination teach or suggest an association between the hTERT mRNA comprising a β-region coding sequence and the presence of cancer cells. Moreover, neither Kilian, Nakamura-2, Hisatomi, Meyerson, Stratagene nor Cech alone or in any combination teach or suggest the primers and probes used in the claimed method and kit for detection and quantitation of hTERT β-region mRNA. Therefore, the references do not teach each and every element of Claims 21 and 28-45. Applicants respectfully request that the rejection to Claims 21 and 28-45 under 35 U.S.C. §103(a) be withdrawn. Applicants submit that Claims 21 and 28-45 meet the requirement for patentability under 35 U.S.C. §103(a).

CONCLUSION

Applicants submit that Claims 21, 28-33 and 35-49 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 21, 28-33 and 35-49 to issuance is therefore kindly solicited.

No fees in addition to the extension fee are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP U.S. Deposit Account No. 16-1150.

Respectfully submitted,

Date: September 27, 2002

42,983

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EXHIBIT A
Claim Amendment: Version with Markings to Show Changes Made

21. (Twice amended) A method for identifying the presence of cancerous cells in a human sample wherein said method comprises:

(a) determining the quantity of hTERT mRNA comprising β-region coding sequence in said sample and in a control sample of non cancerous cells by:

(1) contacting RNA from said sample and said control sample with a pair of primers, wherein said pair of primers consists of a first primer [capable of hybridizing] which hybridizes within exon 8 [or downstream of exon 8] of the hTERT gene and a second primer [capable of hybridizing] which hybridizes within, upstream or downstream of exon 8 of the hTERT gene;

(2) amplifying the nucleic acid sequence;

(3) measuring the generation of amplification products;

(4) determining the quantity of hTERT mRNA comprising β-region coding sequence in said sample from the results obtained in step (3); and

(b) identifying the presence of cancerous cells in said sample if the quantity of hTERT mRNA comprising β-region coding sequence in said sample is greater than the quantity of hTERT mRNA comprising β-region coding sequence in said control sample.

28. (Amended) The method of Claim 21, wherein said second primer [is capable of hybridizing] hybridizes [within exon 6] upstream of exon 7 of the hTERT gene.

29. (Amended) The method of Claim [21] 28, wherein said second primer [is capable of hybridizing] hybridizes within exon [7] 6 of the hTERT gene.

30. (Amended) The method of Claim 21, wherein said second primer is SYC1118 (SEQ ID NO:5), [or] SYC1076 (SEQ ID NO:2) or SYC1078 (SEQ ID NO:3).

31. (Amended) The method of Claim 21, wherein the [first] second primer [is capable of hybridizing] hybridizes within exon 8.

32. (Amended) The method of Claim [31] 21, wherein said first primer is SYC1097 (SEQ ID NO:4).

33. (Amended) The method of Claim 21, wherein the [first] second primer [is capable of hybridizing] hybridizes within exon 9.

38. (Twice amended) A kit for identifying cancerous cells in a human sample, comprising a pair of primers, wherein said pair of primers consists of a first primer [capable of hybridizing] which hybridizes within exon 8 [or downstream of exon 8] of the hTERT gene and a second primer [capable of hybridizing] which hybridizes within, upstream or downstream of exon 8 of the hTERT gene and instructions for identifying cancerous cells.

39. (Amended) The kit of Claim 38, wherein said second primer [is capable of hybridizing within] hybridizes upstream of exon 7 of the hTERT gene.

40. (Amended) The kit of Claim [38] 39, wherein said second primer [is capable of hybridizing] hybridizes within exon 6 of the hTERT gene.

41. (Amended) The kit of Claim 38, wherein said second [primers are] primer is SYC1118 (SEQ ID NO:5), [or] SYC1076 (SEQ ID NO:2) or SYC1078 (SEQ ID NO:3).

42. (Amended) The kit of Claim 38, wherein said first [primers are] primer is SYC1097 (SEQ ID NO:4) [or SYC1078 (SEQ ID NO:3)].

43. (Amended) The kit of Claim 38, further comprising a probe [capable of hybridizing] which hybridizes at a sequence encompassing the exon 7-exon 8 splice junction.